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(54) **ISOXAZOLE DERIVATIVES.**

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(73) Proprietor: **Yoshitomi Pharmaceutical Industries, Ltd.**
35 Hiranomachi 3-chome Higashi-ku
Osaka-shi Osaka 541 (JP)

(72) Inventor: **KAWAKITA, Takeshi**
7-8, Chuoma-chi 1-chome
Nakatsu-shi, Oita 871 (JP)
Inventor: **MURO, Tomio**
631-7, Oaza-kakize Nakatsu-shi
Oita 871 (JP)
Inventor: **SETOGUCHI, Michihide**
5-21, Chuomachi 2-chome
Nakatsu-shi, Oita 871 (JP)

(74) Representative: **Heunemann, Dieter Dr.**
VOSSIUS VOSSIUS TAUCHNER HEUNEMANN
RAUH P.O. Box 86 07 67 Siebertstrasse 4
D-8000 Munich 86 (DE)

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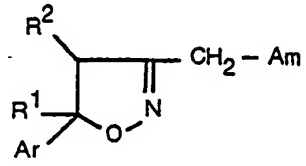
Description

Technical Field and Disclosure of the Invention

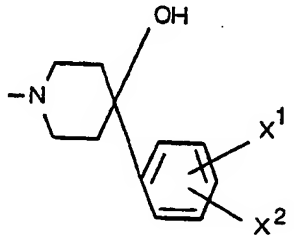
This invention relates to novel isoxazole derivatives having spontaneous locomotor suppressing activity, anti-apomorphine activity and similar activity which are useful as drugs such as psychotropic and antiemetic agents and are represented by the general formula



(I)

to pharmaceutically acceptable acid addition salts thereof, and to a process for preparing these compounds.

In the foregoing formula, Ar represents a phenyl group optionally containing a lower alkoxy group or a halogen atom as a substituent, or a pyridyl group, R^1 represents a hydrogen atom, a lower alkyl group or a group represented by Ar, R^2 represents a hydrogen atom or alternatively R^1 and R^2 are bound together and form a carbon-carbon bond, and Am represents an amino residue selected from the group consisting of the following residues:



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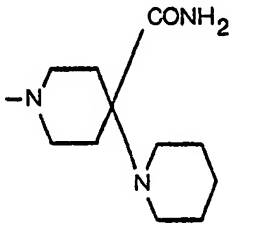

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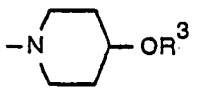

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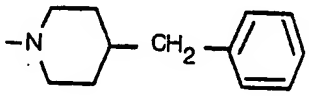

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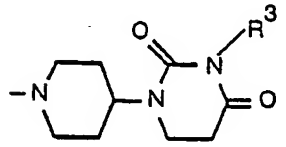

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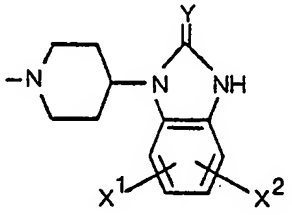

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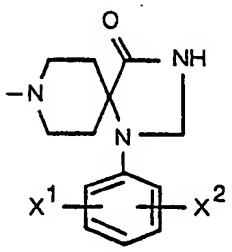

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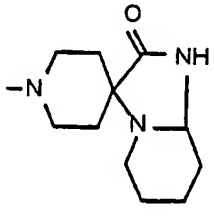

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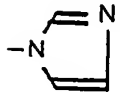

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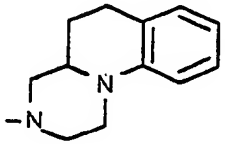
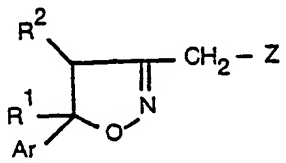


wherein R^3 represents a hydrogen atom or a lower alkyl group, X^1 and X^2 each represent a hydrogen atom, a halogen atom or a trifluoromethyl group, and Y represents O or S.

The term "halogen" herein includes fluorine, chlorine and bromine. The term "lower alkoxy" herein represents a methoxy, ethoxy, propoxy and butoxy. The term "lower alkyl" herein represents methyl, ethyl, propyl and butyl.

DE—OS 2 245 971 discloses isoxazole derivatives that are intermediates for preparing pharmaceutical substances. US—PS 3 890 323 discloses phenylketone derivatives that show central nervous system depressing activity.

The compounds of the formula (I) may be prepared by reacting a compound of the formula



(II)

wherein Ar, R^1 and R^2 are as defined above and Z represents a halogen atom or an organic sulfonyloxy group (e.g. tosyloxy or mesyloxy), with a compound of the formula

H—Am (III)

wherein Am is as defined above.

The reaction may be carried out usually in a solvent such as methanol, ethanol, isopropanol, benzene, toluene, xylene, dimethylformamide, chloroform, dichloroethane, acetone or methyl ethyl ketone, at a temperature between room temperature and 140°C, preferably between 50°C and 110°C, in the presence of potassium carbonate, sodium carbonate, triethylamine or other acid acceptors, for 1 to 48 hours, preferably 4 to 18 hours. The reaction may be accelerated by the use of a catalyst. Examples of such catalyst are potassium iodide and sodium iodide.

The compound of the formula (I) may be converted into an acid addition salt. Typical examples of such an acid addition salt which is pharmaceutically acceptable are salts formed with the aid of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, maleic acid, oxalic acid, succinic acid, fumaric acid, acetic acid, lactic acid and citric acid.

The experiments carried out for demonstrating the anti-apomorphine activity of the compounds of this invention in mice will be described below.

Experimental method:

Groups of 5 male dd-mice (20—25 g body weight) each were used. Apomorphine hydrochloride (0.5 mg/kg) was subcutaneously administered 60 minutes after oral administration of the test compound. Immediately after the apomorphine treatment, motor activity was determined for 20 minutes by animex. For the control groups, 0.5% methylcellulose solution was administered instead of the test compound. The ED_{50}, a dose which inhibited the motor activity by 50% was compared with the control, was determined.

Results:

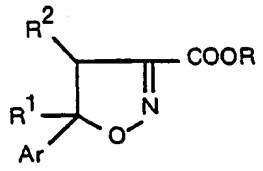
Compound	Anti-apomorphine activity ED_{50} (mg/kg, p.o.)
A	1.7
B	2.1
C	3.4
Clozapine	10

A: 1 - [5 - (4 - Fluorophenyl) - 4,5 - dihydroisoxazol - 3 - ylmethyl] - 4 - (2 - oxo - 1 - benzimidazolinyl)piperidine fumarate

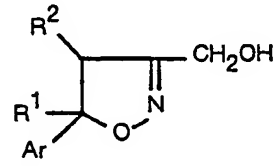
B: 1 - [5 - (4 - Fluorophenyl) - 4,5 - dihydroisoxazol - 3 - ylmethyl] - 4 - (5 - fluoro - 2 - oxo - 1-benzimidazolinyl)piperidine maleate

C: 1 - [5 - (4 - Fluorophenyl) - 4,5 - dihydroisoxazol - 3 - ylmethyl] - 4 - (4 - chlorophenyl) - 4-hydroxypiperidine fumarate

The compounds of the formula (II) are novel and may be prepared, for example, by reducing a compound of the formula



wherein Ar, R^1 and R^2 are as defined above and R represents a lower alkyl group, using sodium borohydride and reacting the resulting compound of the formula



wherein Ar, R^1 and R^2 are as defined above, with thionyl chloride, phosphorus tribromide or similar halogenating agents or tosyl chloride, mesyl chloride or similar organic sulfonating agents.

Reference Example 1

To a solution of 7 g of ethyl 5-phenyl-4,5-dihydroisoxazol-3-ylcarboxylate in 70 ml of methanol, cooled with ice, are added 1.5 g of sodium borohydride in small portions with stirring. After 4 hours have passed, the solvent is distilled off under reduced pressure and the residue is extracted with ethyl acetate. The extract is washed with water, dried and the solvent is evaporated. The crystalline residue thus obtained is recrystallized from isopropyl ether, giving 3-hydroxymethyl-5-phenyl-4,5-dihydroisoxazole in the form of white crystals. Melting point: 73—74°C.

Reference Example 2

3-Hydroxymethyl-5-phenyl-4,5-dihydroisoxazole (3.2 g) is dissolved in 50 ml of anhydrous ether. To the solution cooled with ice are added slowly, dropwise 2.6 g of thionyl chloride under stirring. The reaction mixture is allowed to stand overnight at room temperature and the solvent is then distilled off to give 3-chloromethyl-5-phenyl-4,5-dihydroisoxazole in the form of a yellow brown oil.

The compounds of the formula (I) are used in combination with a suitable and conventional pharmaceutically acceptable excipient in the form of a pharmaceutical composition. The pharmaceutical composition may be configured in the usual form such as tablets, capsules, powders, granules or injection solutions.

When administered for pharmaceutical uses, the compounds of this invention may, for example, be formulated into a pharmaceutical composition as follows.

Tablets (10 mg) may be prepared from the following ingredients:

Compound (I) or salt thereof	10 mg
Lactose	53 mg
Crystalline cellulose	15 mg
Corn starch	20 mg
Polyvinyl alcohol	1.5 mg
Magnesium stearate	0.5 mg
	100 mg

A compound (I) or a salt thereof, crystalline cellulose and corn starch are mixed together and the mixture is then kneaded with 5% polyvinyl alcohol. The resulting mixture is granulated, dried and the dry granules are passed through a 24-mesh screen. The fine granules are mixed with magnesium stearate to form granules for the preparation of tablets. Tablets are prepared by compressing the granules on punches (6.5 mm, 7.0R).

The dose of the compounds of the formula (I) ranges from 0.005 to 100 mg/kg body weight/day, preferably from 0.01 to 50 mg/kg body weight/day, which may be administered at one time or at

several times, although variable depending on the age, body weight and/or severity of the conditions to be treated or response to the medication.

This invention will be better understood from the following examples.

Example 1

3 - Chloromethyl - 5 -phenyl - 4,5 - dihydroisoxazole (5.87 g), 6.3 g of 4 - (4 - chlorophenyl) - 4-hydroxypiperidine, 4 g of potassium carbonate and 50 ml of ethanol are heated to 60—70°C under stirring for 6 hours. The reaction mixture is filtered and the filtrate is condensed by distillation under reduced pressure. To the residue are added 200 ml of ethyl acetate and 100 ml of water. The organic layer is separated off, washed with water, dried on magnesium sulfate and evaporated under reduced pressure. The residue thus obtained is dissolved in isopropyl ether and alcoholic hydrochloric acid is added to the solution. The crystals thus formed are filtered and then recrystallized from isopropyl alcohol, giving 1-(5-phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(4-chlorophenyl)-4-hydroxypiperidine hydrochloride. Melting point: 175—176° (decomposition).

Example 2

3 - Chloromethyl - 5 - (4 - fluorophenyl) - 4,5 - dihydroisoxazole (40 g), 52 g of 4 - (5 - chloro-2 - oxo - 1 - benzimidazolinyl)piperidine, 30 g of potassium carbonate, 15 g of potassium iodide and 1 liter of ethanol are heated to a temperature of 70 to 75°C with stirring for 48 hours. The reaction mixture is then filtered and the mother liquor is condensed under reduced pressure. To the residue are added 800 ml of chloroform and 500 ml of water and the mixture is stirred. The organic layer is separated off, washed with water and dried on magnesium sulfate, and the solvent is distilled off. To the resulting residue are added 130 ml of acetone and 100 ml of isopropyl ether. The crystals thus precipitated are filtered and recrystallized from a mixture of acetone (400 ml) and isopropyl ether (450 ml), to give 67.5 g of 1-[5-(4-fluorophenyl)-4,5-dihydroxyisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine having a melting point of 163 to 164°C. The hydrochloride of this compound melts at 216°C (decomposition).

A 46.5 g-quantity of the above compound (free base) is dissolved in 200 ml of ethanol, and a solution of 15 g of L-tartaric acid in 200 ml of water is added to the ethanol solution. The resulting mixture is allowed to stand at room temperature. The crystals thus precipitated are recrystallized three times from ethanol-water (6:4) to give tartrate monohydrate as colorless prisms. The tartrate monohydrate is treated with an aqueous solution of sodium bicarbonate to give (-)-1-[5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine. Melting point: 143—145°C. $[\alpha]_D^{25}$: — 108.8 (chloroform).

The (+)-isomer of the above compound is obtained in the same manner as above using D-tartaric acid. Melting point: 142—144°C. $[\alpha]_D^{25}$: +112.6 (chloroform).

Example 3

3 - Chloromethyl - 5 - (4 - fluorophenyl - 4,5 - dihydroisoxazole (3.2 g), 3.5 g of 4 - oxo - 1-phenyl-1,3,8-triazaspiro[4,5]decane, 2.1 g of potassium carbonate and 100 ml of ethanol are refluxed for 7.5 hours while stirring. The resulting reaction mixture is filtered and the mother liquor is concentrated. To the residue obtained are added 100 ml of water and the mixture is extracted with ethyl acetate. The extract is washed with water and dried on magnesium sulfate and the solvent is distilled off under reduced pressure. The resulting residue is dissolved in a small amount of alcohol and alcoholic hydrochloric acid is added to the solution. The crystals thus precipitated are filtered and recrystallized from methanol to give 5-(4-fluorophenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]decan-8-ylmethyl)-4,5-dihydroisxazole hydrochloride. Melting point: 219°C (decomposition).

The following compounds may be prepared in the same manner as in the preceding Examples.

1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine
Melting point of 1/2 fumarate: 147—148°C

1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine
Melting point of fumarate: 206°C (decomp.)

1-[5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of hydrochloride: 244°C (decomp.)

1-[5-(3-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of maleate: 197°C (decomp.)

1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of maleate: 201°C (decomp.)

1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-carbamoyl-4-piperidino-piperidine
Melting point of dihydrochloride: 234°C (decomp.)

1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-benzylpiperidine
Melting point of hydrochloride: 184°C

1-(5-Methyl-5-phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of maleate: 218°C (decomp.)
5-Phenyl-3-[4-oxo-1-(4-bromophenyl)-1,3,8-triazaspiro-[4,5]-decan-8-ylmethyl]-4,5-dihydroisoxazole
Melting point of maleate: 221°C (decomp.)
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-hydroxypiperidine
Melting point of maleate: 115—119°C
1'-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-1,2,3,5,6,7,8,8a-octahydro-2-oxoimidazo[1,2-a]-pyridine-3-spiro-4'-piperidine
Melting point of dihydrochloride: 223°C (decomp.)
1-[5-(4-Chlorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of hydrochloride: 230°C (decomp.)
1-[5-(4-Methoxyphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
Melting point of hydrochloride: 229°C (decomp.)
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-thioxo-1-benzimidazolinyl)piperidine
Melting point of 1/2 fumarate: 208—209°C
1-(5-Phenyl-4,5-dihydroisoxazole-3-ylmethyl)-4-methoxypiperidine
Melting point of hydrochloride: 162—164°C
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-carbamoyl-4-piperidino-piperidine
Melting point of dihydrochloride: 158°C (decomp.)
1-(5-Phenyl-4,5-dihydoisoxazol-3-ylmethyl)-4-benzylpiperidine
Melting point of hydrochloride: 208°C (decomp.)
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-oxo-1-benzimidazolinyl)piperidine
Melting point of fumarate: 206°C (decomp.)
1-[5-(2-Pyridyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine
Melting pont of maleate: 188°C
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine
Melting point of hydrochloride: 229°C (decomp.)
5-(Phenyl-3-(4-oxo-1-phenyl-1,3,8-triazaspiro[4,5]-decan-8-ylmethyl)-4,5-dihydroisoxazole
Melting point of hydrochloride: 226°C (decomp.)
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine
Melting point of maleate: 204°C (decomp.)
1-(5-Phenyl-3-isoxazolinylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine
Melting point of hydrochloride: 250°C (decomp.)
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-imidazole
Melting point of fumarate: 110—111°C
1-[5-(2-Pyridyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(3-methyl-2,4-dioxo-1-hexahydropyrimidinyl)piperidine
Melting point of maleate: 169°C (decomp.)
1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)-piperidine
Melting point of fumarate: 125°C (decomp.)
1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-thioxo-1-benzimidazolinyl)piperidine
1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(2-oxo-1-benzimidazolinyl)piperidine
Melting point: 197—199°C
1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-piperidine
1-(5,5-Diphenyl-4,5-dihydroisoxazol-3-ylmethyl)-4-hydroxy-4-(4-chlorophenyl)piperidine
Melting point: 153—154°C
1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)piperidine
Melting point: 199—200°C
1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)-piperidine
1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine
1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)piperidine

1-[5,5-Bis(4-fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-hydroxy-4-(4-chlorophenyl)-piperidine

Melting point: 163—164°C

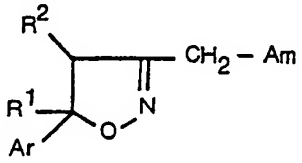
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidine

3-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-2,3,4,4a,5,6-hexahydro-1H-pyrazino-[1,2-a]-quinoline

Melting point of oxalate: 148°C (decomp.)

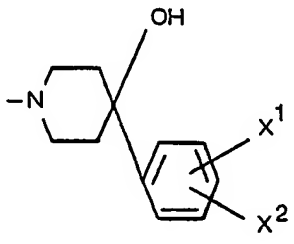
Claims

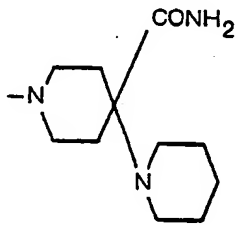
1. An isoxazole derivative represented by the formula

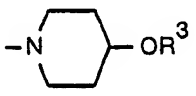


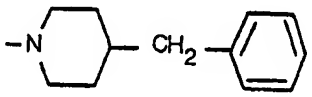
(I)

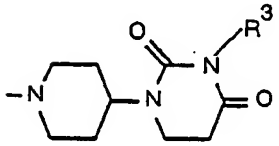
or salts thereof wherein Ar represents a phenyl group which may optionally be substituted with a halogen atom or a C_{1-4} alkoxy group, or a pyridyl group R^1 represents a hydrogen atom, a C_{1-4} alkyl or a group represented by a group Ar, R^2 represents a hydrogen atom, or alternatively R^1 and R^2 are bound together and form a carbon-carbon bond, and Am represents an amino residue selected from the group consisting of the following residues:

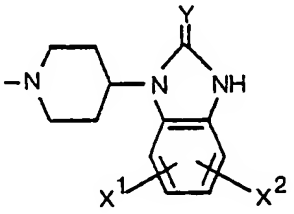


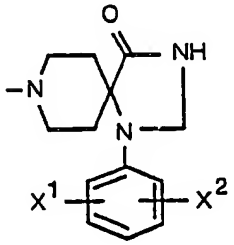


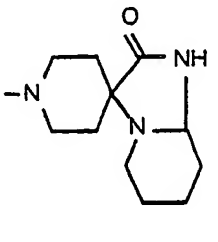


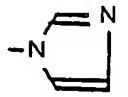




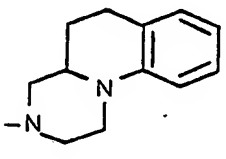








and



wherein R^3 represents a hydrogen atom or a C_{1-4} alkyl group, X^1 and X^2 each represent a hydrogen atom, a halogen atom or a trifluoromethyl group and Y represents O or S.

2. The compound of claim 1:
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-piperidine.

3. The compound of claim 1:
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidine.

4. The compound of claim 1:
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-piperidine.

5. The compound of claim 1:
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine.

6. The compound of claim 1:
5-(4-Fluorophenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro-[4,5]-decan-8-ylmethyl)-4,5-dihydroisoxazole.

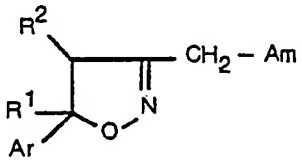
7. The compound of claim 1:
1-[5-(4-Fluorophenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)-piperidine.

8. The compound of claim 1:
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl-4-(5-chloro-2-thioxo-1-benzimidazolinyl)piperidine.

9. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

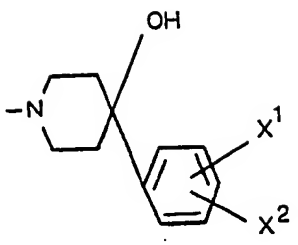
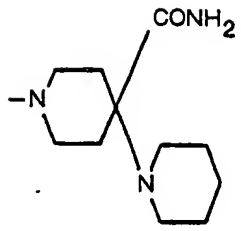
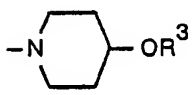
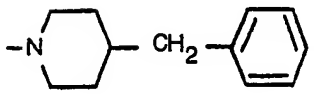
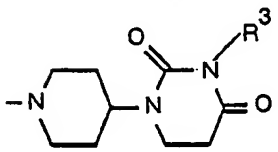
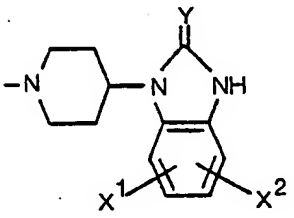
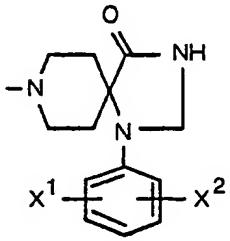
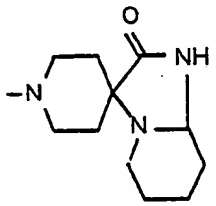
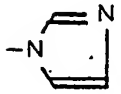
Revendications

1. Dérivé isoxazole, caractérisé en ce qu'il est représenté par la formule générale ci-après



(I)

ou ses sels, dans laquelle Ar représente un groupe phényle qui peut éventuellement être substitué avec un atome d'halogène ou un groupe alkoxy en C_1 à $_4$, ou un groupe pyridyle, R^1 représente un atome d'hydrogène, un radical alkyle en C_1 à $_4$ ou un groupe représenté par le groupe Ar, R^2 représente un atome d'hydrogène, ou, dans une variante, R^1 et R^2 peuvent être reliés et former une liaison carbone-carbone, et Am représente un résidu amino choisi dans le groupe formé par les résidus suivants: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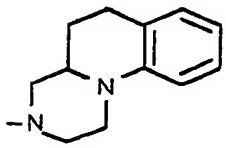


où R^3 représente un atome d'hydrogène ou un groupe alkyle en C_1 à $_4$, X^1 et X^2 sont chacun un atome d'hydrogène, un atome d'halogène ou un groupe trifluorométhyle et Y représente un atome de —O— ou —S—.

2. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-[5-(4-fluorophényl)-4,5-dihydroisoxazol-3-ylméthyl]-4-(5-chloro-2-oxo-1-benzimidazolinyl)-pipéridine.

3. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-[5-(4-fluorophényl)-4,5-dihydroisoxazol-3-ylméthyl]-4-(2-oxo-1-benzimidazolinyl)pipéridine.

4. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-[5-(4-fluorophényl)-4,5-dihydroisoxazol-3-ylméthyl]-4-(5-fluoro-2-oxo-1-benzimidazolinyl)-pipéridine.

5. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-[5-(4-fluorophényl)-4,5-dihydroisoxazol-3-ylméthyl]-4-(4-chlorophényl)-4-hydroxypipéridine.

6. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 5-(4-fluorophényl)-3-(4-oxo-1-phényl-1,3,8-triazaspiro-[4,5]-décan-8-ylméthyl)-4,5-dihydroisoxazole.

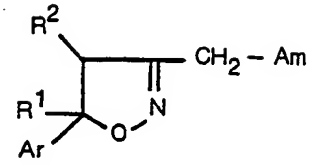
7. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-[5-(4-fluorophényl)-4,5-dihydroisoxazol-3-ylméthyl]-4-(2-thioxo-1-benzimidazolinyl)-pipéridine.

8. Composé selon la revendication 1, caractérisé en ce qu'il s'agit de la: 1-(5-phényl-4,5-dihydroisoxazol-3-ylméthyl-4-(5-chloro-2-thioxo-1-benzimidazolinyl)pipéridine.

9. Composition pharmaceutique, caractérisée en ce qu'elle comprend un composé selon la revendication 1 et un excipient acceptable du point.du vue pharmaceutique.

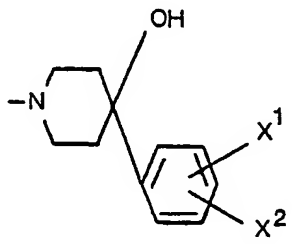
Patentansprüche

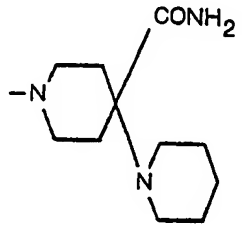
1. Ein Isoxazolderivat der Formel

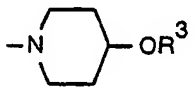


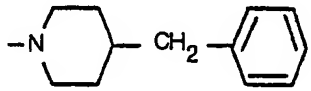
(I)

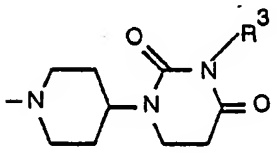
oder seine Salze, in der Ar eine gegebenenfalls durch ein Halogenatom oder einen C_{1-4}-Alkoxygruppe substituierte Phenylgruppe oder eine Pyridylgruppe bedeutet, R^1 ein Wasserstoffatom, eine C_{1-4}-Alkylgruppe oder den Rest Ar bedeutet, R^2 ein Wasserstoffatome darstellt, oder R^1 und R^2 zusammen eine Kohlenstoff-Kohlenstoffbindung darstellen, und Am einen Aminorest bedeutet, der ausgewählt ist aus der Gruppe der folgenden Reste:

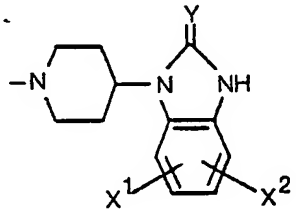


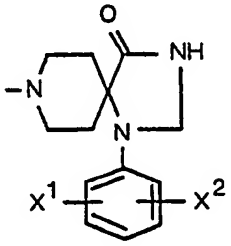


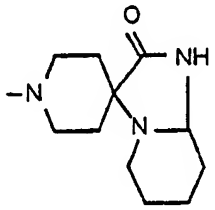


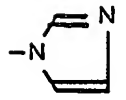












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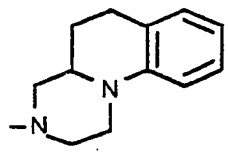

in denen R^3 ein Wasserstoffatome oder eine C_{1-4}-Alkylgruppe bedeutet, X^1 und X^2 jeweils ein Wasserstoffatom, ein Halogenatom oder eine Trifluormethylgruppe darstellen und Y O oder S bedeutet.

2. Die Verbindung nach Anspruch 1:
1-[5-(4-Fluorphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-chlor-2-oxo-1-benzimidazolinyl)-piperidin.

3. Die Verbindung nach Anspruch 1:
1-[5-(4-Fluorphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-oxo-1-benzimidazolinyl)piperidin.
4. Die Verbindung nach Anspruch 1:
1-[5-(4-Fluorphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(5-fluor-2-oxo-1-benzimidazolinyl)-piperidin.
5. Die Verbindung nach Anspruch 1:
1-[5-(4-Fluorphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(4-chlorphenyl)-4-hydroxypiperidin.
6. Die Verbindung nach Anspruch 1:
5-(4-Fluorphenyl)-3-(4-oxo-1-phenyl-1,3,8-triazaspiro-[4,5]-decan-8-ylmethyl)-4,5-dihydroisoxazol.
7. Die Verbindung nach Anspruch 1:
1-[5-(4-Fluorphenyl)-4,5-dihydroisoxazol-3-ylmethyl]-4-(2-thioxo-1-benzimidazolinyl)piperidin.
8. Die Verbindung nach Anspruch 1:
1-(5-Phenyl-4,5-dihydroisoxazol-3-ylmethyl-4-(5-chlor-2-thioxo-1-benzimidazolinyl)piperidin.
9. Ein Arzneimittel, enthaltend eine Verbindung nach Anspruch 1 und einen pharmazeutisch verträglichen Trägerstoff.